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FEE TRANSMITTAL
For FY 2006

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 500.00

Complete if Known	
Application Number	09/896,032-Conf. #2111
Filing Date	June 29, 2001
First Named Inventor	Christoph Seidel
Examiner Name	T. M. Brown
Art Unit	1648
Attorney Docket No.	NY-HUBR 1067.3-DIV (10105485)

METHOD OF PAYMENT (check all that apply)

☒ Check ☐ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): _____

☐ Deposit Account Deposit Account Number: 50-0624 Deposit Account Name: Fulbright & Jaworski L.L.P.

For the above-identified deposit account, the Director is hereby authorized to: (check all that apply)

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FEE CALCULATION (All the fees below are due upon filing or may be subject to a surcharge.)

1. BASIC FILING, SEARCH, AND EXAMINATION FEES

	FILING FEES		SEARCH FEES		EXAMINATION FEES		
Application Type	Fee ($)	Small Entity Fee ($)	Fee ($)	Small Entity Fee ($)	Fee ($)	Small Entity Fee ($)	Fees Paid ($)
Utility	300	150	500	250	200	100	
Design	200	100	100	50	130	65	
Plant	200	100	300	150	160	80	
Reissue	300	150	500	250	600	300	
Provisional	200	100	0	0	0	0	

2. EXCESS CLAIM FEES

Fee Description	Fee ($)	Small Entity Fee ($)
Each claim over 20 (including Reissues)	50	25
Each independent claim over 3 (including Reissues)	200	100
Multiple dependent claims	360	180

Total Claims	Extra Claims	Fee ($)	Fee Paid ($)
4 - 20 =		x	=

HP = highest numer of total claims paid for, if greater than 20.

Indep. Claims	Extra Claims	Fee ($)	Fee Paid ($)
4 - 4 =		x	=

HP = highest numer of independent claims paid for, if greater than 3.

Multiple Dependent Claims

Fee ($)	Fee Paid ($)

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets	Extra Sheets	Number of each additional 50 or fraction thereof	Fee ($)	Fee Paid ($)
- 100 =	/50	(round up to a whole number) x		=

4. OTHER FEE(S)

	Fees Paid ($)
Non-English Specification, $130 fee (no small entity discount)	
Other (e.g., late filing surcharge): 1402 Filing a brief in support of an appeal	500.00

SUBMITTED BY

Signature	Norman D. Hanson	Registration No. (Attorney/Agent)	30,946	Telephone	(212) 318-3168
Name (Print/Type)	Norman D. Hanson			Date	April 13, 2006

Fee Transmittal

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the U.S. Postal Service as Express Mail, Airbill No. EV 793661626 US, on the date shown below in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Dated: April 13, 2006 Signature: Fani Malikouzakis (Fani Malikouzakis)

25645431.1

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the U.S. Postal Service as Express Mail, Air bill No. EV 793661626 US, on the date shown below in an envelope addressed to: MS Appeal Brief - Patents, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Dated: 4/13/06 Signature: Fani Malikouzakis
(Fani Malikouzakis)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Christoph Seidel et al.

Application No.: 09/896,032 Confirmation No.: 2111

Filed: June 29, 2001 Art Unit: 1648

For: METHOD FOR DETERMINING EARLY HCV SEROCONVERSION Examiner: T. M. Brown

APPEAL BRIEF
(37 C.F.R. § 41.37)

MS Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Applicants hereby file this Brief on Appeal in connection with the Notice of Appeal, received by the USPTO on March 13, 2006. Hence, this Brief is timely filed.

This Brief is accompanied by the fee prescribed by 37 C.F.R. § 41.37(a)(2), 41.20(b)(2).

Pursuant to 37 C.F.R. § 41.37(i)(1), the following items are presented.

I. REAL PARTY IN INTEREST

The Real Party In Interest is Roche Diagnostics GmbH, the successor in interest to Boehringer Mannheim, GmbH, the original assignee of the subject application.

II. RELATED APPEALS, INTERFERENCES, AND JUDICIAL PROCEEDINGS

No prior or pending appeals, interferences, or judicial proceedings are known to appellants, appellants' legal representatives, or assignee, which may be directly related to, directly affect, be directly affected by, or have a bearing on the Board's decision in this appeal.

III. STATUS OF CLAIMS

At present, only claims 40-48 are pending. All have been finally rejected, and the rejections of all of these claims are appealed.

NOTE THAT in an Advisory Action dated February 27, 2004, claims 40-48 were allowed (See Evidentiary Appendix). At the time, claims 37-49 were pending.

In response, in an amendment dated March 15, 2004, appellants canceled all claims except allowed claims 40-48 (See Evidentiary Appendix).

Apparently, the Examiner handling the case left the USPTO, and a new Examiner withdrew the allowance in an Office Action dated August 12, 2004, and put forth new rejections.

The application, which is the fourth in a series of case, three of which have issued as U.S. Patents Nos. 6,096,319; 6,306,579; and 6,270,960, was filed on June 29, 2001. Original cliams 1-26 were canceled, and new claims 27-36 were added. Later claims 37-49 were added. Claims 27-39 and 49 were canceled. Only claims 40-48 remain.

IV. STATUS OF AMENDMENTS

The most recent final rejection is dated January 24, 2006. Appeal was taken directly therefrom. No amendments were filed subsequent to the final rejection.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The claimed subject matter is directed to assays for determining so-called hepatitis C virus specific seroconversion antibodies using NS3 proteins modified at a cysteine group. See page 12 of the specification lines 22-26.

Hepatitis C virus, or "HCV" hereafter, is a known, infectious agent. See, e.g., the specification at pages 1-2. The determination of whether an individual is infected with HCV is performed, generally by determining if antibodies to HCV are present in a sample taken from a patient. See, the specification at page 2, lines 11-15, for example.

The claims are directed to assays for determining "seroconversion antibodies." As is discussed, for example, at page 12, lines 27-29 of the specification, determining seroconversion, i.e., antibodies which indicate that a patient has seroconverted is a significant diagnostic markers. Example 5 of the specification, for example at pages 20-21, show the significance of determining seroconversion. As is explained, in Example 5, when the assay of the invention, as described in the claims, was carried out, samples tested with non-modified, NS3 antigen, did not exhibit positivity until day 69. When samples were assayed with modified NS3, however, antibodies were detected as early as day 32. In effect, a subject can begin appropriate therapy sooner than that subject could have had the assay been carried out without modified NS3 protein. DTT (dithiothreitol) is known to modify cysteine residues of proteins, by covalently binding thereto.

Claims 40-42, 44, 45, and 48 all relate to this aspect of the invention, i.e., the use of modified NS3 proteins generally.

Claims 43, 46, and 47 require that the assay for seroconversion use a peptide from a well defined group of peptides. As recited in claim 43, the reactive polypeptide must include amino acids 21-282 of SEQ ID NO: 9, and no more than 20 additional amino acids not found in SEQ ID

NO: 9 or any other HCV protein. Dependent claims 46 and 47 further define the polypeptide used.

VI. GROUNDS OF OBJECTION TO BE REVIEWED ON APPEAL

There is a single ground for rejection set forth in the January 24, 2006 final rejection. The Examiner has rejected all of claims 40-48 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. The rejection is set forth at pages 4-6 of this final rejection.

It is believed that this rejection is erroneous, and the Board is asked to reverse.

VII. ARGUMENT

As alluded to supra, claims 40-42, 44, 45, and 48 all require a modified protein but are not specific as to that protein's amino acid sequence.

Claims 43, 46, and 47 require specific proteins, and specifically call for the use of a modified cysteine or replacement of cysteine by another amino acid.

Hence, for appeal purposes, claims 40-42, 44, 45, and 48 will be argued in one group, while claims 43, 46, and 47 will constitute a second group.

Within the first group, claims 40, 41, 42, 44, 45, and 48 will be argued separately.

Claims 43, 46, and 47 will be argued separately within the second group.

A. ARGUMENTS RELATING TO ENABLMENT GENERALLY

A patent application is presumed to be enabled. The burden is upon the Patent Office, via the Examiner, to show a lack of enablement by a preponderance of the evidence.

The first step in the determination is to review what the specification teaches. As was pointed out, supra, Example 5 of the specification gives particular details pertinent to what is claimed.

Seroconversion assays were carried out, in the presence of the agent DTT, which is known to bind to cysteine residues, thus modifying them. The assays used "HCV-NS3 helicase antigen," which is described throughout the specification, for example, at example 2, page 16.

Agents like DTT react with disulfide bonds in proteins and polypeptides, and these disulfide bonds are formed by interaction of cysteine residues with each other. The antigens in question, i.e., those recited in the claims, are described as being rich in cysteine residues.

The data of example 5 have not been challenged. They show clear superiority of the assays when carried out using modified polypeptides.

In a prior application in this family of cases, i.e., Serial Number 08/892,704, Dr. Ursula-Henrike Wienhues Thelen, submitted a declaration showing that (i) when she modified the polypeptides by covalent attachment of the modifying group, iodoacetate, and (ii) when cysteine residues were substituted by serine residues, the modified polypeptides were more effective in determining seroconversion than non-modified polypeptides. This declaration was re-submitted, in this application, on August 2, 2005. (See Evidentiary Appendix).

With respect to this evidence, the Examiner has offered very little rebuttal. Rather, as provided at page 4 of the Office Action of January 24, 2006, the Examiner concedes enablement for modification with iodoacetate. No discussion is provided, whatsoever, with respect to the experiments on amino acid substitution. Rather, the Examiner's argument appears to boil down to the following statement, taken from page 2 of the January 24, 2006 Office Action:

> "The preceding office action cites numerous references that show cysteine modifications have drastic adverse effects on antibody specificity. Therefore, the unpredictability of cysteine modifications strongly suggests that the claimed modifications are not enabled."

It is not clear to applicants which "previous office action" the Examiner refers to. An Advisory Action, dated April 4, 2005, cites one reference. In a final rejection, dated January 11, 2005, no references were cited. In the Office Action of August 23, 2005, three references were cited, one of which was also cited in the Advisory Action.

The issue is: do these references, taken with the Examiner's argument, succeed in shifting the burden to applicants, i.e., do they overcome the presumption of enablement? Applicants respectfully submit they do not.

Mangold, et al., Virology, 211:535-543 (1995), was cited in the aforementioned Advisory Action, and also in the August 23, 2005 Office Action.

This reference is not prior art, so its availability as a reference against the claims is limited, as a matter of law. See MPEP 2124, for example.

Even taking the reference as a whole, however, applicants submit it is irrelevant. First, the reference deals with a different virus, i.e., Hepatitis B. (The invention deals with Hepatitis C). Further, the Hepatitis B protein with which Mangold et al. worked was the envelope, or "env" protein. See page 535, second column. "Env" proteins are proteins found on the exterior of virus particles. They have an important role in viral function; however, that function differs from internal proteins, such as the helicase protein, which is the subject of the invention. The specification discusses the different roles of protein in virus particles, at page 1, lines 10-15, for example.

Hence, one has a non-prior art reference addressing (i) a different virus, and (ii) an unrelated protein. To the extent that Mangold teaches anything about amino acid substitution, the aforementioned declaration remains more relevant, dealing as it does with the specific virus, and the specific protein, of the invention. The Examiner has taken the position that data cannot be generalized. If that is the case within the confined universe of modified, HCV NS3 proteins, then one can hardly deem it reasonable to take data from a different virus, and a different protein, and apply it as the Examiner has done.

Similarly, Wasenhauer, et al., J. Virol., 67(3):1315-1321 (1993), is not prior art. It, too, deals with the Hepatitis B virus, and with an envelop structural protein, i.e., the "core" protein. As noted supra, the specification, at page 1, lines 10-15, discuss differences in viral proteins. Wasenhauer et al. describe the "enigmatic" secretory core protein. Wasenhauer interestingly enough, discusses how this HBc protein differs from HBc protein by only ten amino acids (page 1315, column 1); however:

"(T)hey exhibit greatly different biophysical properties."

The reference goes on to discuss the different immunological activities of two, related proteins, differing by only 10 amino acids:

> "The HBc protein efficiently assembles into particles and binds to antibodies which arise in virtually all infected individuals very early during infection. These antibodies, termed anti-HBcAg, recognize a linear sequence on the HBc protein (amino acids 74 through 85) which, however, is accessible only in particulate core protein. The HBc protein normally does not form particles and contains other private epitopes which are recognized by antibodies (anti-HBcAg) which arise only late during infection."

See Wasenhauer, page 1313, first column.

The reference relied upon by the Examiner teaches that two, related proteins, from the same organism, differing from each other by only 10 amino acids, have completely different immunoreactivities.

Given this teaching, it is submitted that one of ordinary skill in the art would not draw any conclusions as to how modifications in an unrelated protein, from a different organism, would function. A nexus is required even for prior art references, and such a nexus is simply not present with this reference.

The only reference used by the Examiner which actually qualifies as prior art is Long, et al., J. Virol., 64(11): 5542-5552 (1990), and it is even more irrelevant than the non-prior art materials discussed previously.

Long, et al. worked with "glycoprotein D" which is "a structural component of the virion envelope" of Herpes simplex 1. As with Mangold and Wasenhauer, the molecule studied is a structural one, rather than an internal molecule; however, the source organism is not even a hepatitis virus! There is no art recognized correlation between the family of hepatitis viruses and the family of herpes viruses. Hence, it is submitted that Long is even less relevant than the other references.

Further, what the data in Long provide are somewhat contradictory. These data are summarized at page 5545, "antigenic analysis." The Long paper is interested in determining what happens to unrelated muteins, when expressed at different temperatures, i.e., 31.5°C and 39.5C. The conclusion reached for the experiment is that, for the most part, the folding of proteins was temperature sensitive. There is no discussion within this reference, nor of the non-prior art references, as to what is the impact of modifying cysteines on assays of the type claimed. This, however, is a critical feature of the claimed invention. Any reference which fails to take into account a required feature of the claims cannot be accorded much weight.

The Examiner's entire argument, as presented in the Office Action of August 23, 2005, is based upon conclusions drawn from these references, and as has been shown, supra, they are collectively of little relevance, as dealing with different organisms and unrelated proteins. Two do not even qualify as prior art. The single reference that does quality presents results that are inconclusive.

The Examiner asserts, in this action, that applicants have failed to show that the modifications have predictable effect.

That is not applicants burden. The burden rests on the Examiner to show unpredictability. The showing provided by the Examiner falls short of doing this.

B. CLAIMS 40-42, 45, AND 48

As indicated supra, each of these claims is argued separately.

CLAIM 40

This claim requires modification of a hepatitis C virus, NS3 protein, at a cysteine residue. Nothing in the Examiner's argument supports the contention that this would lead to unpredictable results. Rather, the experiments presented in the specification, and in subsequent declarations, show that the results are, in fact predictable.

CLAIM 41

Claim 41 requires the covalent attachment of a moiety to a cysteine residue. The Examiner agrees that this has been shown, and that the attachment of iodoacetate groups is enabled.

The Examiner then misstates the law, in calling upon applicants to show that additional substances would work. That is not the proper legal standard.

The burden is upon the Examiner to show that additional molecules would not function in the manner claimed. Applicants see no such showing in the references, nor do they see any argumentation presented by the Examiner other than an impermissible attempt to shift the burden to applicants.

CLAIM 42

As has been shown, via declaration, substitution of cysteine residues by serine resulted in a polypeptide which was effective in a seroconversion assay of the type claimed. The Examiner has dismissed these data, and instead argues that data on unrelated proteins, with different functions, are relevant. It has never been the case that such evidence is acceptable for shifting the presumption of enablement unless a proper nexus is shown. That nexus has not been shown.

CLAIMS 44

This claim specifies 4 distinct species of modifying groups, one of which the Examiner agrees is enabled. No evidence has been presented by the Examiner to support his contention that the claim is non-enabled. As the Examiner has not met his burden, the rejection must be reversed.

CLAIM 45

This claim specifies two amino acids as substitutes for cysteine. As has been pointed out, supra, applicants submitted data showing that substitution with serine, which is one of the options, resulted in a protein useful in a functional assay. These data have not been rebutted. Nor has the Examiner submitted any evidence to challenge the presumption of enablement for γ-aminobutyric acid, which is specifically claimed.

CLAIM 48

This claim specifies a distinct defined protein, modified in accordance with claim 41. A claim this specific calls for more than a generic statement as to what has been shown for other, non-related proteins. None has been provided. Applicants respectfully request the rejection be reversed.

C. CLAIMS 43, 46 AND 47

Claim 43 requires a subgenus of specific polypeptides, defined by an amino acid sequence spelled out in the claim, plus a modification.

As has been shown, supra, applicants have shown enablement with both modifying groups, and cysteine substitution. A specific family of polypeptides, with defined sequences, is required.

The Examiner has not provided the specific evidence of lack of enablement required for a claim of this type.

D. CLAIMS 46 AND 47

These claims further define the polypeptide used. They are even more specific than claim 43. As such, even more specific evidence is required, to rebut the presumption of enablement. It has not been provided. The rejection should be reversed.

VIII. CLAIMS

A copy of the claims involved in the present appeal is attached hereto as Appendix A.

IX. EVIDENCE

Advisory Action dated February 27, 2004;

Amendment dated March 15, 2004;

Declaration dated August 2, 2005.

X. RELATED PROCEEDINGS

No related proceedings are referenced in II above, or copies of decisions in related proceedings are not provided, hence no Appendix is included.

XI. CONCLUSION

For the reasons set forth, supra, it is believed that the rejection of claims 40-48 under 35 U.S.C. § 112, first paragraph, as not being supported by an enabling disclosure is believed improper and should be reversed.

Respectfully submitted,

By _____

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Evidentiary Appendix
Claims Appendix

CLAIMS APPENDIX
(37 C.F.R. § 41.37(C)(VIII)

Listing of Claims on Appeal

Claim 40. A method for determining hepatitis C virus specific seroconversion antibodies, comprising incubating a human sample suspected to be a seroconversion sample containing hepatitis C virus specific antibodies taken from a subject with at least one polypeptide consisting of an amino acid sequence found in hepatitis C virus protein NS3 region, which is immunologically reactive with said hepatitis C virus specific seroconversion antibodies, and determining binding of said antibodies to said polypeptide to recognize seroconversion in said subject, wherein said polypeptide has been modified at at least one cysteine residue.

Claim 41. The method of claim 40, wherein said cysteine residue has been modified by covalent attachment of a modifying group.

Claim 42. The method of claim 40, wherein said cysteine residue has been replaced by another amino acid.

Claim 43. A method for determining hepatitis C virus specific seroconversion antibodies, comprising incubating a human sample suspected to be a seroconversion sample containing hepatitis C virus specific antibodies taken from a subject with at least one polypeptide consisting of an amino acid sequence found in hepatitis C virus protein NS3 region, which is immunologically reactive with said hepatitis C virus specific seroconversion antibodies, and determining binding of said antibodies to said polypeptide to recognize seroconversion in said subject, wherein said polypeptide consists of (a) at least amino acids 21-282 of SEQ ID NO: 9, and (b) a contiguous sequence of less than 20 amino acids that is not found in hepatitis C virus proteins, wherein (b) has been concatenated to the N or C terminus of (a) wherein at least one cysteine of said polypeptide is modified either by replacing it with another artificial or natural amino acid, or by a modifying group.

Claim 44. The method of Claim 41, wherein said modifying group is maleimidodioctylamine, N-methly-maleinimide, iodoacetic acid, and iodoacetamide.

Claim 45. The method of claim 42, wherein said cysteine residue has been replaced by serine, or γ-aminobutyric acid.

Claim 46. The method of claim 43, wherein said polypeptide consists of at least amino acids 19 to 290 of SEQ ID NO: 9, and no more than amino acids 9 to 300 of SEQ ID NO: 9.

Claim 47. The method of claim 43, wherein said polypeptide consists of at least amino acids 16 to 293 of SEQ ID NO: 9, and no more than amino acids 12 to 297 of SEQ ID NO: 9.

Claim 48. The method of claim 41, wherein said polypeptide consists of amino acids 14 to 295 of SEQ ID NO: 2.

EVIDENTIARY APPENDIX
(37 C.F.R. § 41.37(C)(IX)

Advisory Action dated February 27, 2004;

Amendment dated March 15, 2004; and

Declaration dated August 2, 2005.

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/896,032	06/29/2001	Christoph Seidel	HUBR-1067.3 DIV	2111

24972 7590 02/27/2004

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666 FIFTH AVE
NEW YORK, NY 10103-3198

EXAMINER	
WORTMAN, DONNA C	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 02/27/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action

Application No.	Applicant(s)	
09/896,032	SEIDEL ET AL.	
Examiner	**Art Unit**	
Donna C. Wortman, Ph.D.	1648	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 14 Jan 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.

4. ☒ Newly proposed or amended claim(s) *40-48* would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☐ The a)☐ affidavit, b)☐ exhibit, or c)☐ request for reconsideration has been considered but does NOT place the application in condition for allowance because: _____.

6. ☒ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: *40-48*.

   Claim(s) objected to: _____.

   Claim(s) rejected: *37-39 and 49*.

   Claim(s) withdrawn from consideration: _____.

8. ☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☐ Other: _____

Donna C. Wortman, Ph.D.
Primary Examiner
Art Unit: 1648

Claims 37, 40, 43, 46, and 47 were proposed to be amended in the amendment after final submitted 14 January 2004.

The amendment has been entered.

Objection and rejection withdrawn

The entry of the after final amendment overcomes the objection of claims 40-48 set out in the final rejection on page 5 as being dependent on a rejected base claim. Claims 40-48 are allowed.

The amendment to claim 37 to recite "human" has overcome the rejection under 35 U.S.C. 103(a) as being unpatentable over JP06074956 in view of Beach et al. (Journal of Medical Virology 3643):226-227, 1992).

Rejections maintained

Regarding the rejections of claims 39 and 49 under 35 U.S.C. 112, second paragraph; claims 39 and 49 under 35 U.S.C. 102(b)/103(a) over JP06074956; claim 37 under 35 U.S.C. 103(a) over JP06074956 in view of Vallari et al. (Journal of Clinical Microbiology 30(3):552-556, 1992); and claim 38 under 35 U.S.C. 103(a) over JP06074956 in view of Vallari et al. and of US Patent Re. 32,696 to Schuurs et al., Applicant's remarks and arguments have been noted but have not been found persuasive as they rely on the newly submitted Declaration of Dr. Wienhues-Thelen. The Declaration has not been considered since it is not directed solely to issues that were newly raised by the Examiner in the final rejection. Claims 37, 38, 39 and 49 remain rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donna C. Wortman, Ph.D. whose telephone number is 571-272-0913. The examiner can normally be reached on Monday-Thursday, 7:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Donna C. Wortman, Ph.D.
Primary Examiner
Art Unit 1648

dcw

CERTIFICATE OF EXPRESS MAIL

"Express Mail" mailing label # EV 331559067 US

Date of Deposit March 15, 2004

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service on the date indicated above and is addressed to the Commissioner of Patents, Mail Stop: Patent Application, P.O. Box 1450, Alexandria, VA 22313-1450.

Name of Depositor: Fani Malikouzakis

Signature of Depositor: Fani Malikouzakis

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	:	Christoph SEIDEL et al.
Serial No	:	09/896,032
Filed	:	June 29, 2001
For	:	METHOD FOR DETERMINING EARLY HCV SEROCONVERSION
Art Unit	:	1648
Examiner	:	Donna C. Wortman

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT

SIR:

Please amend this application as follows:

IN THE CLAIMS

Claims 1-39. (Cancelled).

Claim 40. (Previously presented) A method for determining hepatitis C virus specific seroconversion antibodies, comprising incubating a human sample suspected to be a seroconversion sample containing hepatitis C virus specific antibodies taken from a subject under reducing conditions which prevent formation of covalent, cross linked molecular aggregates with at least one polypeptide consisting of an amino acid sequence found in hepatitis C virus protein NS3 region, which is immunologically reactive with said hepatitis C virus specific seroconversion antibodies, and determining binding of said antibodies to said polypeptide to recognize seroconversion in said subject, wherein said polypeptide has been modified at at least one cysteine residue.

Claim 41. (Previously presented) The method of claim 40, wherein said cysteine residue has been modified by covalent attachment of a modifying group.

Claim 42. (Previously presented) The method of claim 40, wherein said cysteine residue has been replaced by another amino acid.

Claim 43. (Previously presented) A method for determining hepatitis C virus specific seroconversion antibodies, comprising incubating a human sample suspected to be a seroconversion sample containing hepatitis C virus specific antibodies taken from a subject under reducing conditions which prevent formation of covalent, cross linked molecular aggregates with at least one polypeptide consisting of an amino acid sequence found in hepatitis C virus protein NS3 region, which is immunologically reactive with said hepatitis C virus specific seroconversion antibodies, and determining binding of said antibodies to said polypeptide to recognize

seroconversion in said subject, wherein said polypeptide consists of (a) at least amino acids 21-282 of SEQ ID NO: 9 and (b) a contiguous sequence of less than 20 amino acids that is not found in hepatitis C virus proteins, wherein (b) has been concatenated to the N or C terminus of (a), or an isolated polypeptide which is at least 90% homologous thereto, wherein at least one cysteine of said polypeptide is modified either by replacing it with another artificial or natural amino acid, or by a modifying group.

Claim 44. (Previously presented) The method of Claim 41, wherein said modifying group is maleimidodioctylamine, N-methly-maleinimide, iodoacetic acid, and iodoacetamide.

Claim 45. (Previously presented) The method of claim 42, wherein said cysteine residue has been replaced by serine, or γ- aminobutyric acid.

Claim 46. (Previously presented) The method of claim 43, wherein said polypeptide consists of at least amino acids 19 to 290 of SEQ ID NO: 9, and no more than amino acids 9 to 300 of SEQ ID NO: 9.

Claim 47. (Previously presented) The method of claim 43, wherein said polypeptide consists of at least amino acids 16 to 293 of SEQ ID NO: 9, and no more than amino acids 12 to 297 of SEQ ID NO: 9.

Claim 48. (Previously presented) The method of claim 41, wherein said polypeptide consists of amino acids 14 to 295 of SEQ ID NO: 2.

Claim 49. (Cancelled)

REMARKS

This amendment presented in accordance with the comments made by the Examiner in her Advisory Action, should place this application in condition for allowance.

A Notice of Allowance is requested.

Respectfully submitted,

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Christoph SEIDEL et al.
Serial No.	:	08/892,704
Filed	:	July 15, 1997
For	:	RECOMBINANT ANTIGEN FROM THE NS3 REGION OF THE HEPATITIS C VIRUS
Art Unit	:	1643
Examiner	:	J. Williams

DECLARATION UNDER 37 C.F.R. § 1.132 OF URSULA-HENRIKE WIENHUES-THELEN

Ursula-Henrike Wienhues-Thelen, declares as follows:

(i) I am one of the co-inventors in the above-identified application. Attachment 1 is my *curriculum vitae*.

(ii) I am familiar with the present application, and I have read and understood this application.

(iii) I supervised certain experiments as described below and conclude as follows:

The results reported herein demonstrate that modifying the cysteine residues of the hepatitis C virus (HCV) polypeptide of the present invention as is taught in the present specification at pages 4-5 with a covalent modifying group (Example 1, discussed *infra*), or replacing the cysteine residues of the polypeptide of the present invention as is taught on page 5 of the specification with other natural or artificial amino acids (Example 2, discussed

infra), substantially increases the overall sensitivity of the method claimed in claims 29-32 by increasing the immunological reactivity of the polypeptide with HCV antibody. In addition, the results (Example 3, below) show that the concentration of releasable sulfhydryl groups of non-modified and modified HCV helicase antigen under reducing conditions may be readily determined.

Accordingly, the specification provides sufficient guidance to enable one skilled in the art to practice the invention claimed in claims 29-32 without the exercise of undue experimentation.

Methods and Materials

Example 1. Modification of the HCV antigen by Covalent Attachment of a Modifying Group

Cysteine residues of the HCV helicase antigen were modified by iodoacetate according to procedures well known in the art. The immunological reactivity of the modified HCV helicase antigen versus unmodified HCV helicase antigen with anti-HCV-positive human sera was determined using the double-antigen bridge test as set forth in Example 5 of the specification.

Results

As shown in Attachment 2, the covalently modified HCV helicase antigen was more specific for the antibodies in anti-HCV-positive human serum compared to the unmodified HCV helicase antigen. Accordingly, the modification of cysteine residues at HCV polypeptides considerably increased the overall sensitivity of a method for detecting anti-hepatitis C virus antibodies.

Example 2. Modification of the HCV Antigen by Replacement of Cysteine Residues with Another Amino Acid.

In this experiment, cysteine residues of the HCV helicase antigen were substituted for serine residues by site-specific mutagenesis. The reactivity of modified versus unmodified HCV helicase antigen with anti-HCV-positive human sera was determined using the double antigen bridge test as set forth in Example 5 of the specification.

Results

As shown in Attachment 3, the mutagenized HCV helicase antigen was more specific for the antibodies in the serum compared to the unmodified antigen. Accordingly, the polypeptides with substituted cysteine residues increased the overall sensitivity of a method for detecting anti-hepatitis C virus antibodies.

Example 3. Method of Determining the Concentration of Releasable Sulfhydryl Groups

An aliquot of the helicase to be examined is mixed with 20 mM DTT and incubated at 37°C for 1 hour.

The reducing agent is separated off by means of chromatography using Sephadex G-25 or by dialysis against 0.1 M sodium phosphate buffer, pH 6.0, 0.1% SDS.

0.25 mg helicase are then diluted to 1 ml with 0.15 M sodium phosphate buffer, pH 7.6, 2mM EDTA and mixed with 0.03 ml of a DTDP solution (11 mg dithiodipyridine dissolved in 5 mM sodium phosphate buffer, pH 6.0, 1mM EDTA).

The mixture is incubated at 25°C for 2 minutes, then the extinction is photometrically measured at 334 nm. The extinction is corrected by the reagent blank value (DTDP in

sample buffer without helicase) and the sample blank value (helicase in sample buffer without DTDP).

The concentration of the sulfhydryl groups is then computed by means of Lambert-Beer's Law (ε_{334nm} = 15.2 cm x $nmol^{-1}$).

Results

Attachment 4 shows the concentration of releasable sulfhydryl groups of modified and non-modified HCV helicase antigen under reducing conditions. Cysteine-modified antigens contain less sulfhydryl groups which are releasable under reducing conditions.

In conclusion, the above results demonstrate that the modification of cysteine residues by covalent attachment of a modifying group or replacement of cysteine residues by another amino acid, significantly increases the sensitivity of the method for detecting HCV antibody as claimed in claims 29-32, as evidenced by the increased immunological reactivity of modified helicase antigen with anti-HCV-positive human sera.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

5.5.1998
Date

Ursula-Henriette Uhlenhaut

CURRICULUM VITAE

name:	Ursula-Henrike Wienhues-Thelen
day of birth:	15.09.1959
place of birth:	Cologne
1965-1969:	primary school in Cologne
1969-1978:	secondary school in Cologne
16.june 1978:	final examination
october 1978:	start with the study of biology at the university of Cologne
03.october 1980:	„Vordiplom“
march-april 1982:	research work with professor K. Willecke at the institute of cellbiology at the university, Uniklinikum Essen
jan. - sept. 1983:	research work with professor W. Doerfler at the institute of genetics in Cologne
31.october 1984:	finishing diploma thesis in professor W.Doerfler´s laboratory
march - may 1987:	research work with professor K.Hosokawa at the Kawasaki Medical School in Okayama / Japan
07.may 1988:	finishing doctor thesis in professor W.Doerfler´s laboratory
1988 - 1991:	postdoc in professor W.Neupert`s laboratory in the Institut für Physiologische Chemie in Munich
since september 1991:	development of diagnostica, Boehringer Mannheim GmbH, Tutzing

München,
16.03.1998 Ursula-Henrike Wienhues-Thelen

Example regarding covalently modified cysteines

Evaluation of the reactivity of differently modified helicase antigens with anti-HCV-positive human sera

	Reactivity of helicase antigen, without chemical modification of the cysteines cut off index	Reactivity of helicase antigen the cysteines of which are chemically modified with a protective group: iodine acetate (IAA) cut off index
Serum 1	20.9	33.2
Serum 2	15.1	24.4
Serum 3	4.0	14.5

Carried out in analogy to Example 5.

Example regarding the replacement of cysteines by other amino acids

Evaluation of the reactivity of differently modified helicase antigens with anti-HCV-positive human sera

	Reactivity of helicase antigen, without chemical modification of the cysteines cut off index	Reactivity of helicase antigen having mutagenized cysteines (all but two cys residues are serine) cut off index
Serum 1 (early seroconversion)	0.9	11.3

SH status of rec. HCV helicase, HCV helicase mutein and derivatives

Helicase	Modification	SH groups releasable under reducing conditions
HCV helicase, underivatized	none	6.4
HCV helicase, biotinylated	chemically with IAA	2.8
HCV helicase, ruthenylated	chemically with IAA	3.8
HCV helicase mutein	cysteine replacement	1.9
HCV helicase mutein, biotinylated	cysteine replacement	0.15
HCV helicase mutein, ruthenylated	cysteine replacement	0.6